MALT lymphoma meets stem cells

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Mucosa-associated lymphoid tissue (MALT) lymphomas are a distinct clinico-pathologic entity mainly associated with chromosomal translocations involving the MALT1 gene. Therefore, these chromosomal rearrangements have been traditionally used to identify tumor MALT lymphoma B-cells, and they have always been detected in differentiated tumoral B cells. However, the hematopoietic progenitor and stem cells (HS/PCs) seem not to show any of the translocations detected in tumor B cells, although these aberrations would be difficult to detect if the frequency of these putative stem cells harboring the translocation was low. These results would seem to suggest that the MALT lymphoma cell-of-origin, in which the oncogene activation takes place (as a result of the mentioned chromosomal rearrangement), is not a stem/progenitor cell. However, until now, all the experiments targeting the expression of human MALT1 oncogene to the mouse B-cell compartment have failed to reproduce the human disease in mice.1 Therefore, it is potentially possible that, in human patients, the occurrence of MALTassociated oncogenic alterations might happen in the (HS/PCs) compartment, and this cell-of-origin adopts/acquires afterwards a MALT lymphoma cell fate as a consequence of the MALT1 activity. To elucidate if MALT lymphoma is a stem cell-driven tissue, we developed mice in which we limited MALT1 expression to the Sca1+ cells (Sca1-MALT1 mice).2 Sca1-MALT1 mice developed clonal extranodal B-cell lymphomas recapitulating not only the main clinical, histopathological and molecular features of human MALT lymphomas, but also the progression to the aggressive form of human ABC-DLBCL. These data demonstrate that human MALT lymphoma pathogenesis can be modeled in mice by targeting MALT1 expression to the HS/PCs compartment, suggesting that a similar scenario may occur in human MALT lymphomas. In human MALT lymphoma, like in all human cancers due to clonal nature of the disease, the genetic oncogenic alteration is present in all the cellular types that compose the tumoral tissue, from the cancer cell-of-origin to the terminal differentiated tumor B-cells. In our stem cell-driven Sca1-MALT1 model, the system has been designed to ensure that the expression of the MALT1 oncogene is restricted to the stem/progenitor compartment. In these conditions, the expression of the oncogene in the HS/ PCs population is nevertheless capable of generating a full-blown MALT lymphoma with all its differentiated cellular components. Of course, the demonstration that MALT lymphoma development can be established in mice by limiting MALT1 oncogene expression to Sca1+ cells implies that abolishing oncogene function in the differentiated MALT lymphoma tumor cells does not interfere with their generation. This suggests that MALT1 enforces a regulatory program in stem cells that, in some way, is capable of persisting during hematopoiesis and of imposing a tumor phenotype characteristic of MALT lymphoma, an observtion that seems to apply to other cancer-initiating gene defects.3-9 Therefore, we hypothesize that MALT1 mediates tumorigenesis through epigenetic/genetic modification of target genes that remain in this modified state in the mature tumor, even in the absence of MALT1 expression, in agreement with a reprogramming role for MALT1 in regulating MALT lymphoma formation.

This MALT1-mediated reprogramming is, however, permissive, in that it allows the normal differentiation of all hematopoietic cell types and only reveals its malignant nature in the B cell compartment. In the oncogenic reprogramming model presented here, the reprogrammed Sca1+ population can nevertheless complete a multistage differentiation pathway involving an initial commitment to the B cell lineage and a subsequent differentiation to tumor MALT lymphoma cells. This model of cancer is very informative with respect to the fact that the oncogenic mutations can have different roles in CSC vs. differentiated cancer cells and explains why targeted therapies can eliminate the latter without affecting the former. Indeed, our Sca1-MALT1 model suggests that the molecular mechanisms of action of MALT1 at the stem cell level will probably be different from those acting at later stages of tumoral cell differentiation. But perhaps the most crucial question is, how does MALT1 instruct stem cells to give rise to a malignant MALT lymphoma cell? In order to identify the genes that are associated with MALT1-induced reprogramming of stem cells, we performed a supervised analysis of the transcriptional profiles of HS/PCs purified from Sca1- MALT1 mice and control mice. The data identified a set of genes that are reproducibly differentially regulated in MALT1- targeted stem cells vs. control stem cells, showing that Sca1-MALT1-derived HSCs presented an abnormal expression of lymphoid-related genes, presumably reflecting their cell-intrinsic priming into the lymphoid lineage. Overall, these results show that enforced MALT1 expression restricted to stem cells is all that is required to generate tumoral MALT cells in mice, therefore suggesting for the first time a role for stem/progenitor cells in the pathogenesis of MALT lymphomas. To our knowledge, these results represent the most convincing evidence to date that MALT lymphoma can arise and be driven by a cell fate change within the stem cells. The major questions that arise in light of these findings are how MALT1 oncogene reprogramming impacts on the target cell, and what are the qualitative and/or quantitative figures that make stem/progenitor target cells more vulnerable to malignancy. However, the technical approach used here to demonstrate that the stem cell compartment drives the pathogenesis of MALT lymphoma is not sufficiently stringent to conclusively rule out that expression from the transgene is limited to stem cells, as it would be difficult to definitely exclude that low levels of expression at certain transitional stages in the mature compartments were at the root of the malignancy. Mouse models of cancer where precise control of the timing of the oncogene exposure is possible10-12 will be instrumental to address these and other questions to understand the complexity of stem-associated cancers.